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Seed
701 Fifth Avenue Suite 6300
Seattle, WA 98104-7092

EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 07/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/744,866	AUSTRUP ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,10,22 and 23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,10,22 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 12, 2004 has been entered.

2. The amendment filed April 12, 2004 is acknowledged and has been entered. Claims 1, 3, 4, and 10 have been amended. Claim 23 has been added.

3. Claims 1-7, 10, 22, and 23 are pending in the application and are currently under prosecution.

Grounds of Objection and Rejection Withdrawn

4. Unless specifically reiterated below, Applicant's amendment filed April 12, 2004 has obviated the grounds of objection and rejection set forth in the previous Office action mailed June 10, 2003.

Specification

5. The specification is objected to because of the apparent omission of Tables I and II, referred to at page 40, lines 12-19, which reportedly contain a description of the results of the isolation process exemplified by Examples 1 and 2 at pages 35 and 36.

The international application PCT/EP/99/05386 filed 27 July 1999, which is part of the record, notably does not include either Table I or Table II; and the published document WO 0/06702 A1 (10 February 2000) also does not include either table, although references to the tables are made in the paragraph at page 38, line 32, through page 39, line 1. The absence of either table in these documents suggests that the attempt

to incorporate the tables in the instant application would introduce new matter and thereby violate the written description requirement set forth under 35 USC § 112, first paragraph.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claim 10 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-7, 10, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a written description rejection.

The claims are drawn to a method for isolating disseminated tumor cells, whereby the isolated disseminated tumor cells are free from the separating agent, which comprises

a ligand. The claims are therefore directed to the use of a genus of separating agents, which commonly comprise a ligand usable for the isolation of disseminated tumor cells.

At page 19, lines 19-21, the specification describes the separating agent used as "antibodies, lectins, etc."

The disclosure of the invention would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed, because the written description of the genus of separating agents to which the claims are directed would not be adequate to enable the skilled artisan to immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of separating agents to which the claims are directed. The members of the genus of separating agents are expected to have widely varying structures and functions, just as lectins and antibodies have markedly different structure and function.

MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:

> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was

complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

In addition, in deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of separating agents by only their common ability be used in the process of isolating disseminated tumor cells does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what

the members of genus must be capable of doing, not of the substance and structure of the members.

10. Claims 1-7, 10, 22, and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-7, 10, 22, and 23 are drawn to a method for isolating disseminated tumor cells from a bodily fluid comprising passing a body fluid or part thereof through a screen, whereby the disseminated tumor cells that are retained on the screen "are free from a separating agent that comprises a ligand for isolation" and are essentially unchanged by the isolation process.

The amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation to provide isolated disseminated tumor cells, which are free from the separating agent used and which more particularly are in a biological state, as opposed to an artificial state, such that the isolated cells are left essentially unchanged by the isolation process. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The Nature of the Invention:

The invention, as claimed, is a method for isolating disseminated tumor cells from a body fluid, such that the isolated disseminated tumor cells are free from a separating agent used in the process of isolation, which according to Applicant's disclosure of the

invention provides isolated disseminated tumor cells that are unchanged by the isolation process.

The State of the Prior Art:

The prior art teaches methods for isolating disseminated tumor cells from a body fluid, which comprise passing the fluid or part thereof through a screen.

The prior art teaches particular methods comprising modifying the disseminated tumor cells contained in the body fluid by attaching to the cells a specific separation agent, e.g., an antibody conjugated to a paramagnetic beads, passing the fluid or part thereof through a porous screen, such that the disseminated tumor cells attached to the separation agent is retained on the screen, and detaching the disseminated tumor cells from the separation agent used by, e.g., enzymatically cleaving a labile bond adjoining the antibody and the paramagnetic bead; see, e.g., Rye et al. (*American Journal of Pathology* **150**: 99-106, 1997) (of record). The modified cells are retained on the porous material by virtue of the relatively larger size of the complex consisting of the modified cell and the separating agent used, which is excluded from entry or passage through the narrower pores. Thus, the prior art teaches methods that provide isolated disseminated tumor cells, which are free from the separating agent used, but not necessarily in a biological state that is essentially unchanged by the isolation process, since at least a portion of the separating agent remains attached to the isolated disseminated tumor cells, depending upon the means by which the detachment is achieved. Furthermore, the means by which the prior art achieves separation of the isolated cells from the separating agent causes a loss of retention on the screen, such that, in the end, the isolated disseminated tumor cells freed of the separating agent used are not retained on the screen.

Alternatively, the prior art teaches, for example, that ascitic fluid or a fraction thereof can be enriched for isolated tumor cells growing in clumps by passing the fluid or fraction thereof through a porous nylon mesh filter having pores of a width of 30 μm; see Hirte et al. (*Gynecologic Oncology* **44**: 223-226, 1992) (of record). The clumps of cells are retained on the porous material by virtue of their relatively larger size, which is excluded from entry or passage through the narrower pores. However, the prior art teaches that single cells and relatively small cell aggregates pass through the filter and

thus are not retained on the filter, which is porous to the relatively small individual cells and cell aggregates.

Collectively, the prior art teaches that disseminated tumor cells can be isolated from bodily fluids, e.g., blood and bone marrow, provided the tumor cells are part of clumps or aggregates large enough to be retained by a sieve or if the tumor cells are selectively modified by attaching a relatively large separating agent, such as an antibody conjugated to a paramagnetic or glass bead.

The Relative Skill of those in the Art:

Although high, the relative skill of those in the art is such that, absent a sufficient disclosure to enable the use of the claimed invention, an undue amount of additional experimentation would need be performed before the claimed invention, commensurate in scope with the claims, can be used to isolate disseminated tumor cells free from the separating agent used in the isolation process, such that the isolated disseminated tumor cells are unchanged by the isolation process.

The Amount of Direction or Guidance Disclosed in the Specification:

The specification teaches that the disseminated tumor cells provided as isolates from a body fluid or part thereof can be free of the separating agent, e.g., an antibody or a lectin, which is used in isolating the cells according to the disclosed method; see, e.g., page 19, lines 16-21. The specification discloses that the isolated disseminated tumor cells that are free of the separating agent used are in a biological state, as opposed to an artificial state (page 19, lines 21-25). The specification further discloses that the biological state of the isolated disseminated tumor cells, which are free of the separating agent used, is "a state which the relevant cell may adopt in a body fluid of a human or non-human animal individual, in particular relation to physiology, morphology and /or expression profile" (page 19, lines 25-29). The specification discloses that parameters relating to the cell cycle, activation, proliferation, and apoptosis are important for describing the biological state of the isolated disseminated tumor cells, which are free of the separating agent used (page 19, lines 30-32). The specification discloses, "said parameters are left essentially unchanged by the isolating process of the invention" (page 19, liens 32-34).

However, the specification fails to teach how isolated disseminated tumor cells, which are retained on the screen, are made free of the separating agent used, where a separating agent is used, whether the separating agent comprise an antibody or a lectin.

Regarding the screen, the specification teaches the screen can have pores of a diameter ranging from as small as 10 mm to as large as 200 mm (page 8, lines 37-39). The specification teaches the screen can be composed of a large variety of material, including nylon (page 9, line 23, through page 11, line 2).

However, the specification fails to teach of which material a screen should be made, and how large the pores should be, to isolate various and different tumor cells, which may have varying diameters, depending upon the type of cell from which the tumor was derived.

The Presence or Absence of Working Examples:

Example 1 at pages 35 and 36 of the specification apparently teaches that disseminated tumor cells can be isolated from blood as part of a fraction of mononuclear cells, which are retained on a screen having pores with a diameter of 20 μm. Due to the apparent omission of Tables I and II, which are referred to at page 40, lines 12-19, it is not possible to ascertain the extent to which the resultant fraction is enriched for disseminated tumor cells, or to ascertain the purity of the disseminated tumor cells retained by the screen. The specification does not exemplify the use of a screen having pores of other diameters in the range of 15 to 30 μm.

Example 2 at page 36 teaches isolating CD45+ cells from blood by a process comprising attaching to the cells an anti-CD45 antibody conjugated to a paramagnetic bead.

Example 3 at pages 36-39 describes the genetic analysis of the isolated cells contained in various fractions produced by the isolation process exemplified by Examples 1 and 2.

Example 4 at pages 39 and 40 describes the results of the genetic analysis of the isolated cells contained in the various fractions produced by the isolation processes. Although Tables I and II have been omitted, at page 40, lines 19-25, the specification discloses that the results acquired showed that disseminated tumor cells had been isolated

by the process described from the blood acquired from 5 of 15 patients diagnosed with carcinomas or melanoma.

Example 5 at pages 40 and 41 teaches isolating disseminated tumor cells from the blood of a patient having breast cancer and the blood of a patient having colon cancer according to the process exemplified in Example 2. Notably, in the instance of the blood acquired from the patient diagnosed with breast cancer, the specification discloses that the isolated disseminated tumor cells were not proliferative (page 41, lines 11 and 12). Because cancer cells are generally proliferative, it is presumed that the isolation process, contrary to the assertion that the invention provides essentially unchanged isolated disseminated tumor cells, altered the isolated disseminated breast cancer cells.

There is a notable absence of exemplification of the use of screens made of different materials and of screens having pores of differing diameters, since the disclosed exemplification is limited to the use of a screen composed of a woven mesh of PE threads, which has pores of a diameter of 20 μm (see page 35, lines 24-27). Accordingly, the amount of exemplification is not reasonably commensurate in scope with the claims.

The Predictability or Unpredictability of the Art:

In view of the teachings of Hirte et al. (cited *supra*), for example, the skilled artisan could not predict whether a screen made of a material, other than a woven mesh of PE threads, and having pores of a diameter, other than of a diameter of 20 μm, can be used to isolated disseminated tumor cells from a bodily fluid, such as blood or bone marrow. As noted above, Hirte et al. teaches that individual tumor cells and relatively small aggregates of tumor cells are not retained by a nylon filter having pores of 30 μm. Therefore, while the specification teaches that a woven mesh of PE threads having pores of a diameter of 20 mm can be used to isolated disseminated tumor cells by retention on the mesh, the skilled artisan cannot predict whether a screen composed of a different material or having pores of a different diameter can be used effectively to isolate such cells by retention.

The Breadth of the Claims:

The claims are drawn to a method comprising the use of a screen composed of a large genus of materials; furthermore, the claims encompass the use of a screen having a widely varying pore size.

In addition, while the claims encompass a method for isolating disseminated tumor cells by passing the cells through a screen, such that the cells are retained on the screen, the claims also encompass a method comprising attaching to disseminated tumor cells a separating agent comprising an antibody or a lectin, passing the modified cells through a screen, such that the modified cells are retained on the screen, and freeing the cells retained on the screen from the separating agent used, such that the isolated disseminated tumor cells retained on the screen are free of the separating agent used.

The Quantity of Experimentation Required:

An undue amount of additional experimentation would have to be performed before the claimed invention, reasonably commensurate in scope with the claims, could be practiced successfully by the skilled artisan, since the skilled artisan cannot predict whether a screen composed of a material other than a woven mesh of PE threads having a pore diameter of 20 mm can be used effectively to isolate disseminated tumor cells by the process exemplified in Example 1 at pages 35 and 36, and yet the claims encompass the use of a screen composed of widely varying materials and having widely differing pore diameters.

An undue amount of additional experimentation would have to be performed before the claimed invention could be used to isolate disseminated tumor cells, which are retained by the screen and which are free of the separating agent used, such that the cells are essentially unchanged by the isolation process, because the skilled artisan would have to devise a means to free the isolated disseminated tumor cells, which are retained on the screen, from the separating agent used without altering the natural biological state of the cells and without creating an artificial state. While the prior art teaches means by which the isolated cells might be freed of the separating agent used in the isolation process, these means provide a cell that is not unaltered by the process, since the cell retains at least a portion of the separating agent used. Furthermore, in addition to freeing the isolated cells from the separating agent used, these means will generally cause a loss of

retention on the screen, such that, in the end, the isolated disseminated tumor cells freed of the separating agent used are not retained on the screen.

Furthermore, by virtue of their isolation alone, the isolated disseminated tumor cells would be set in an artificial state, rather than a natural biological state; even so, the specification discloses at page 41, lines 11 and 12, that isolated disseminated breast cancer cells isolated by the process exemplified are not proliferative, which the specification indicates at page 19, lines 30-32, suggests that contrary to the assertion, the isolated cells have been altered by the isolation process. In contrast, the specification discloses that isolated disseminated colon cancer cells, which were isolated using the claimed invention, were proliferative. In view of these disclosures, because the skilled artisan cannot predict whether any particular type of disseminated tumor cells (i.e., apart from disseminated colon cancer cells) can be isolated by the disclosed method without altering the natural biological state of the cells, the skilled artisan would have to perform an undue amount of additional experimentation to determine whether the claimed invention can actually provide isolated disseminated tumor cells of any particular type, which are unaltered by the isolation process.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation to provide isolated disseminated tumor cells, which are free from the separating agent used and which more particularly are in a biological state, as opposed to an artificial state, such that the isolated cells are left essentially unchanged by the isolation process.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 10 provides for the use of a screen having a mesh or pore width of about 15 to 30 μm, but since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is

indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

14. The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

15. Claims 1-4, 6, 7, 10, 22, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Rye et al. (*American Journal of Pathology* **150**: 99-106, 1997) for essentially the reason set forth in the Office action mailed June 10, 2003.

Claims 1-4, 6, 7, 22, and 23 are drawn to a method for isolating disseminated tumor cells from a cell-containing body fluid, particularly blood or bone marrow, comprising separating cellular components from non-cellular components of the body fluid and passing the part of the fluid containing the cells through a screen having a pore width of about 20 μm, whereby isolated disseminated tumor cells, which are retained on the screen are free from a separating agent used, are provided.

Claim 10 is drawn to the use of a screen having a mesh or pore width of about 15 to 30 μm.

The On-line Medical Dictionary (published at the Dept. of Medical Oncology, University of Newcastle upon Tyne © Copyright 1997-2004 - The CancerWEB Project), which is available on the Internet at http://cancerweb.ncl.ac.uk/omd/, defines "disseminated disease" as follows: "Disease in which the cancerous cells have spread from the tissue of origin to other organs".

As noted previously, Rye et al. teaches a method for isolating disseminated tumor cells from blood, bone marrow, ascitic or pleural fluids, and enzyme-digested tissue biopsies; see entire document (e.g., the abstract). Although Rye et al. does not explicitly refer to the isolated tumor cells as disseminated tumor cells, it is clear that the tumor cells from the blood and bone marrow of the patients had disseminated from breast cancers or malignant melanomas, as the tumor cells were isolated from anatomical site distant from the anatomical site of the primary tumor (see the definition provided above). Rye et al. teaches passing a cell-containing body fluid or part thereof through a screen having pores of a width of 20 microns (μm); see, e.g., the abstract. More particularly, Rye et al. teaches samples were prepared by subjecting peripheral blood and bone marrow specimens to Lymphoprep™ density gradient centrifugation, a process that separates the cellular components of the specimens from non-cellular components (page 100, column 2). The cell pellets were resuspended in a suspension medium, namely Dulbecco's minimal essential medium (page 100, column 2). The suspension of cells was passed through a 20-micron nylon microfilament filter and obtaining a retained fraction of cells comprising the disseminated tumor cells (page 101, column 1). Although Rye et al. teach an additional step, namely incubating the suspension of cells with a primary antibody bound to magnetic beads and magnetically separating tumor cells bound by the antibody from other cells not bound by the antibody (page 101, column 1), was performed before filtration, the specification teaches that such a step can be performed before filtration at page 13, lines 25-32.

In addition, Rye et al. teaches the filter-isolated cells were cultured on the filters in growth medium, such that the isolated disseminated tumor cells grew, i.e., proliferated (page 101, paragraph bridging columns 1 and 2). The progeny of the filter-isolated tumor cells, which grew on the filter, were free of the separating agent used, since the separating

agent could not have detached from the parental cells originally retained on the filter to reattach to the progeny. Alternatively, Rye et al. teaches the filter-isolated can be harvested from the filter, so that the cells can be processed for immunohistochemical analysis as cytospin preparations (page 101, column 2).

Thus, Rye et al. teaches a method for isolating disseminated tumor cells comprising passing a body fluid through a porous screen having pores of a diameter of 20 mm, which provides isolated disseminated tumor cells retained on the screen and free of the separating agent used.

Absent a showing of any difference, the method disclosed by the prior art and the claimed invention are deemed the same.

At pages 4-6 of the amendment filed April 12, 2004, Applicant has traversed the similar ground of rejection under 35 USC § 102(b) set forth in the previous Office action. Applicant has argued that the prior art does not anticipate the claimed invention because the prior art does not teach the isolated disseminated tumor cells are free from a separating agent used in the isolation process.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

At page 101, in the paragraph bridging both columns, Rye et al. teaches the filter-isolated cells were cultured on the filters in growth medium, such that the isolated disseminated tumor cells grew, i.e., proliferated (page 101, paragraph bridging columns 1 and 2). The progeny of the filter-isolated tumor cells, which grew on the filter, were necessarily free of the separating agent used, since the separating agent could not have detached from the parental cells originally retained on the filter to reattach to the progeny. Thus, Rye et al. teaches a method for isolating disseminated tumor cells comprising passing a body fluid through a porous screen having pores of a diameter of 20 μm, which provides isolated disseminated tumor cells retained on the screen and free of the separating agent used. All of the limitations of the claims have been met by the disclosure of Rye et al.

16. Claims 1-4, 6, 7, 10, 22, and 23 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,265,229-B1 for essentially the reason set forth in the Office action mailed June 10, 2003.

As previously noted, US Patent No. 6,265,229-B1 ('229) teaches a method for isolating micrometastatic tumor cells from various bodily fluids, including blood, bone marrow, and effusions, which comprises filtering a suspension of cells through a porous membrane having preferably 20 micron pores and obtaining a retained fraction of cells comprising the disseminated tumor cells; see entire document (e.g., column 4, lines 54-67; column 10, lines 42-47; and column 11, lines 52-60). Although '229 does not explicitly refer to the isolated tumor cells as disseminated tumor cells, it is clear that in practicing the disclosed methods, the tumor cells isolated from the blood or bone marrow of the patients diagnosed with non-hematological malignancies, i.e., breast cancer, would have to have disseminated from the anatomical site of origin, or the primary tumor (see the definition provided in the rejection above). Furthermore, '229 refers to these cells as micrometastatic (see, e.g., column 12, lines 6-14); and it is noted that similarly the specification uses the term "micrometastasized" to refer to a subgenus of disseminated cancer cells at page 7, lines 3-7). In addition, '229 teaches that the specimens of blood and bone marrow may be prepared by density gradient centrifugation, providing the example of Lymphoprep™ density gradient centrifugation, followed by resuspension in a resuspension medium; see, e.g., column 7, lines 19-27.

Furthermore, '229 teaches the separated cells isolated using the filter can be cultured on the filter by placing the filter directly in a culture medium and allowing the isolated cells to divide and grow (column 11, lines 52-60). The progeny of the filter-isolated tumor cells, which grew on the filter, were free of the separating agent used, since the separating agent could not have detached from the parental cells originally retained on the filter to reattach to the progeny.

Additionally, although '229 teaches the disclosed invention provides isolated disseminated tumor cells, which do not need to be removed from the filter, '229 discloses

that the prior art taught the removal of isolated tumor cells from a filter used in the isolation process; see, e.g., column 2, lines 36-48).

Thus, '229 teaches a method for isolating disseminated tumor cells comprising passing a body fluid through a porous screen having pores of a diameter of 20 mm, which provides isolated disseminated tumor cells retained on the screen and free of the separating agent used.

Absent a showing of any difference, the method disclosed by the prior art and the claimed invention are deemed the same.

At pages 6 and 7 of the amendment filed April 12, 2004, Applicant has traversed the similar ground of rejection set forth in previous Office action, arguing that the prior art does not anticipate the claimed invention because the prior art does not teach all the limitations of the claims. In particular, Applicant has argued the prior art does not teach the isolated disseminated tumor cells are free from a separating agent used in the isolation process.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

At page column 11, lines 52-60, '229 teaches the filter-isolated cells can be cultured directly on the filters in growth medium, such that the isolated disseminated tumor cells will divide and grow. The progeny of the filter-isolated tumor cells, which grew on the filter, were necessarily free of the separating agent used, since the separating agent could not have detached from the parental cells originally retained on the filter to reattach to the progeny. Thus, '229 teaches a method for isolating disseminated tumor cells comprising passing a body fluid through a porous screen having pores of a preferable diameter of 20 μm, which provides isolated disseminated tumor cells retained on the screen and free of the separating agent used. All of the limitations of the claims have been met by the disclosure of '229.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. Claims 1, 3, 4, and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Rye et al. (*American Journal of Pathology* **150**: 99-106, 1997) or US Patent No. 6,265,229-B1 in view of Hirte et al. (*Gynecologic Oncology* **44**: 223-226, 1992) (of record).

Rye et al. and US Patent No. 6,265,229-B1 teach that which is set forth above in the respective rejections under 35 USC § 102.

However, neither Rye et al. nor US Patent No. 6,265,229-B1 expressly teach suggest removing the retained disseminated tumor cells from the screen, i.e., the filter "by passing a liquid through the screen in a direction opposite to that in which the body fluid or part thereof or resuspended cell-containing fraction is passed" (claim 5).

Hirte et al. teaches a method for isolating tumor cells from a body fluid or part thereof, which comprises passing the body fluid or part thereof through a porous mesh filter, such that the tumor cells are retained on the filter, and isolating the retained cells by a backwashing; see entire document, particularly the abstract and page 224, column 1.

One of ordinarily skilled in the art at the time of the invention would have understood that the process of backwashing disclosed by Hirte et al. comprises passing a liquid through the filter in a direction opposite to that in which the body fluid or part thereof containing the cells is first passed.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to isolate the disseminated tumor cells retained on the filter after passing the body fluid or part thereof containing the tumor cells through the filter, such the tumor cells are retained on the filter, by backwashing, i.e., passing a liquid through the filter in a direction opposite to that in which the body fluid or part thereof containing the cells is first passed, because both Rye et al. and US Patent No. 6,265,229-B1 teach or

suggest removing the tumor cells retained on the filter for further use of the isolated cells and because Hirte et al. teaches the removal of the tumor cells can be accomplished by such a process. One ordinarily skilled in the art would have been motivated to do so at the time the invention was made to isolate tumor cells free of the filter used in the isolation process so that the cells can be further analyzed by means not so adaptable to cells retained on the filter, such as immunohistochemical analysis on cytospin preparations.

Conclusion

19. No claims are allowed.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
July 14, 2004

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